## MOTHERISK ROUNDS

# The Use of Antidepressants in Pregnancy: Focus on Maternal Risks

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### Abstract

Studies have consistently reported a decrease in the use of antidepressants during pregnancy compared with the pre-pregnancy period. Multiple recent studies have focused on the potential fetal risks of selective serotonin reuptake inhibitors (SSRIs) and selective norepinephrine reuptake inhibitors (SNRIs), with very little attention paid to maternal risks. The maternal risks of these medications are the focus of this review.

Untreated depression is associated with increased risks of maternal morbidity, both somatic and psychiatric. In contrast, use of antidepressants has been associated with increased risks of hypertension, preeclampsia, and bleeding. In this review we present the evidence for maternal risks in an attempt to develop a risk-benefit ratio.

### Résumé

Les études indiquent uniformément une baisse du recours aux antidépresseurs pendant la grossesse, par comparaison avec la période prégrossesse. De multiples études récentes se sont centrées sur les risques fœtaux potentiellement liés aux inhibiteur sélectif du recaptage de la sérotonine (ISRS) et aux inhibiteur sélectif du recaptage de la norépinéphrine (ISRN), tout en ne portant que très peu attention aux risques maternels. La présente analyse est axée sur les risques maternels qui sont liés à ces médicaments.

La dépression ne faisant pas l'objet d'un traitement est associée à des risques accrus de morbidité maternelle, tant somatique que psychiatrique. Par contre, l'utilisation d'antidépresseurs a été associée à des risques accrus d'hypertension, de prééclampsie et de saignement. Dans le cadre de la présente analyse, nous présentons les données dont nous disposons au sujet des risques maternels afin de tenter d'établir un rapport risques-avantages.

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**Key Words:** selective serotonin reuptake inhibitor, SSRI, selective norepinephrine reuptake inhibitor, SNRI, depression, risk, pregnancy

Competing Interests: None declared.

## INTRODUCTION

Major depressive disorder is the second leading cause of burden of disease in women,[1,2] and up to 20% of women of reproductive age are affected by depression.[3] Depression has a prevalence of 12.8% in the second trimester of pregnancy and 12.0% in the third trimester.[3] Hence, large numbers of women may need antidepressant drugs.[4] Different studies suggest that between 1% and 8% of pregnant women use antidepressants.[5–8]

To date, depression remains under-detected and under-treated during pregnancy.[9–12] A major contributor to the degree of under-treatment is concern about potential adverse fetal outcomes as a result of fetal exposure to antidepressants.[7,13]

The objective of this review is to present the evidence for maternal risks in an attempt to develop a risk-benefit ratio.

## SEARCH METHODS

We searched Medline and EMBASE for articles published from inception to July 30, 2013, dealing with maternal complications of depression in pregnancy and postpartum. The following search terms were used: "pregnancy," "depression," "antidepressants," "SSRIs," "SNRIs," "complications," "bleeding," "gestational hypertension," "hypertension," "preeclampsia," "fetus," and "delivery."

Studies were reviewed and data were extracted according to reported effects or lack of effect on maternal health.

## FETAL RISKS

Numerous studies have suggested that use of antidepressants during pregnancy is associated with poor fetal outcomes, including miscarriage, congenital malformations, stillbirth, preterm birth, low birth weight, adverse short term transient neonatal effects, and persistent

pulmonary hypertension in the newborn.[14–38] These studies have been balanced by studies not showing adverse fetal effects.[16,39–42] Interestingly, a large recent study documented an increase in the incidence of ventricular septal defect in babies exposed to antidepressants in the first trimester, but also among babies of mothers with untreated depression.[43]

In contrast, very little attention has been paid to maternal risks associated with depression and SSRIs, and this will be the focus of this review.

## PHARMACOLOGY

The SSRIs and SNRIs regulate mood by inhibition of reuptake of serotonin and norepinephrine, respectively, in related brain regions.[44] All antidepressants cross the placenta in humans, but this fact should not be misinterpreted as evidence of hazard; most medications cross the placenta, and very few have been shown to cause adverse fetal effects.[45] Depression is mostly recurrent, with as much as 90% of affected persons having more than one episode.[46] In non-pregnant women with depression, the likelihood of recovery without medication is approximately 20% in the first week but declines as the duration of depression extends, and after six months the likelihood of recovery is less than 1%.[47,48]

## DEMOGRAPHIC CHARACTERISTICS

Pregnant women with depression are more likely to be older, to have pre-existing diabetes (OR 1.32), chronic hypertension (OR 1.34), or asthma,[49,50] and, not surprisingly, have an increased risk of requiring hospitalization during pregnancy. Pregnant women with depression have a higher prevalence of use of other psychotropic drugs, with the most common being benzodiazepines (8.9%), opioids (6.0%), benzodiazepine-like hypnotics (4.7%), and antipsychotics (3.0%).[49]

## MATERNAL RISKS OF UNTREATED DEPRESSION

Uncontrolled and untreated depression in pregnancy has been associated with increased risks of miscarriage, low birth weight, and prematurity.[50] It has also been linked to gestational hypertension and preeclampsia,[51,52] excessive bleeding,[38] increased uterine artery resistance,[53] and the need for Caesarean section or instrumental vaginal delivery[54]; more subjectively, it is associated with painful labour and therefore more need for epidural analgesia.[55,56] With regard to the fetus and neonate, untreated depression during pregnancy has been associated with low Apgar scores,[57] admission to NICU,[54] and fetal death.[57,58]

In women on antidepressant medication, the effects of withdrawal or discontinuation include affective symptoms, general somatic symptoms, sleep disturbances, and gastrointestinal symptoms, most of which occur within days to weeks of stopping the medication or reducing the dose. Typically, relapse of depression occurs more gradually.[59–63] In a study of 36 pregnant women who called the Motherisk Program in Toronto, the only reason women gave for stopping their prescribed medication was fear that the medication would harm their babies.[64] All the women experienced abrupt discontinuation syndrome, 11 reported suicidal thoughts, and four required hospitalization. One woman had a therapeutic abortion and one replaced benzodiazepine use with alcohol. After counselling, two-thirds of these women renewed their medication within several days. All babies born to women who re-established medication were healthy and normal.[64]

In a study using monthly psychiatric assessments throughout pregnancy, 201 pregnant women were enrolled in three American centres.[61] All participants had a history of major depression prior to pregnancy, were at less than 16 weeks' gestation and had been euthymic for at least three months prior to their last menstrual period. Among the 82 women who maintained their medication throughout pregnancy, 21 (26%) had a relapse of depression, compared with 44 of the 65 women who discontinued medication (68%). Women who discontinued medication relapsed significantly more frequently over the course of their pregnancy (hazard ratio 5.0; 95% CI 2.8 to 9.1, $P < 0.001$).

Postpartum depression is a serious medical emergency that can be often predisposed to untreated depression in late pregnancy.[65,66] Suicide is a leading cause of death among young women, predominantly among women with mental illnesses.[65,66] Untreated depression may also lead to suboptimal infant care, suboptimal mother–child attachment, lack of care of other children, and an adverse relationship with the partner.[48]

## MONITORING SYMPTOMS OF DEPRESSION IN PREGNANCY

While a psychiatrist should be the lead physician taking care of a depressed pregnant woman, screening pregnant women for depressive symptoms could be done easily by an obstetrician or general practitioner. The five-minute

### ABBREVIATIONS

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| SSRI | selective serotonin reuptake inhibitor |
| SNRI | selective norepinephrine reuptake inhibitor |
| TCA | tricyclic antidepressant |